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(17810-705)

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BOARD OF PATENT APPEALS AND INTERFERENCES**

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| Art Unit: | 1632 |
| Examiner: | A-M. Baker |
| Appellants: | Weiss, et al. |
| Serial No.: | 08/486,313 |
| Filed: | June 7, 1995 |
| For: | MULTIPOTENT NEURAL STEM CELL COMPOSITIONS |

Boston, MA 02111
February 28, 2002

**Board of Patent Appeals and Interferences**
Commissioner for Patents and Trademarks
Washington, DC 20231

# APPEAL BRIEF

Sir:

Applicants file this Appeal Brief, in triplicate, pursuant to 37 C.F.R. § 1.192(a), in support of their Notice of Appeal, dated July 30, 2001, along with a petition for a five (5) month extension of time. A check for $980.00 is enclosed to cover the fee for the petition pursuant to 37 C.F.R. § 1.17(a)(5). With the extension, this Appeal Brief is due on or before February 28, 2002. In addition, a check for $160.00 is enclosed to cover the fee for filing a brief in support of an appeal required under 37 C.F.R. § 1.17(c). Further, Applicants have requested concurrently herewith an oral hearing before the Board of Patent Appeals and Interferences, and enclose an additional check in the amount of $140.00 to cover the fee pursuant to 37 C.F.R. § 1.17(d).

The Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to Deposit Account No. 50-0311, Reference 17810-705 DIV 12.

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## REAL PARTY IN INTEREST

The real party in interest is Stem Cells, Inc. (formerly CytoTherapeutics, Inc.), the exclusive licensee of NeuroSpheres Holdings, Ltd., the assignee of the application from all inventors.

## RELATED APPEALS AND INTERFERENCES

An Appeal Brief will also be filed by March 13, 2002 in the related case: U.S.S.N. 08/479,796, Attorney Docket No. CTI-N5 DIV 9 (17810-705 DIV 9), which has claims directed to use of neural stem cell cultures for remyelination.

## STATUS OF CLAIMS

Pending claims 26-27, 32-37 and 39-62, as set forth in Appendix 1, are the subject of this appeal.

## STATUS OF AMENDMENTS

All amendments have been entered. Applicants last amended the claims in a communication to the Patent Office dated April 12, 2000. This Appeal is from a Final Rejection dated January 31, 2001. A response to this rejection was filed on July 30, 2001, with no claim amendments. The Notice of Appeal was also filed July 30, 2001.

## SUMMARY OF INVENTION

The claims are directed to methods for transplanting central nervous system ("CNS") neural stem cell progeny to a host. The CNS neural stem cells and the various methods and uses of these cells claimed in this application and related counterparts are pioneering inventions. Applicants have been widely recognized by the scientific community as the first to identify and isolate CNS neural stem cell cultures, and to teach methods for proliferating and differentiating

those cell cultures, as well as various methods and systems using those cultures (such as the transplantation methods claimed here).

The subject matter of the present application, uses of *in vitro* CNS neural stem cell compositions, has been now been pending since 1991. The present application claims priority to United States Patent Application 07/726,812, filed July 8, 1991, United States Patent Application 07/961,813, filed Oct. 16, 1992; United States Patent Application 07/967,622, filed Oct. 28, 1992; and United States Patent Application 08/010,829, filed Jan. 29, 1993, all now abandoned.

This patent application is one of several related co-pending applications that are based on the same specification. Of those applications, five have issued as United States patents:

(1) USSN 08/483,122 issued as United States Patent No. 5,750,376 on May 12, 1998, with claims directed to genetically modified central nervous system neural stem cell cultures.

(2) USSN 08/486,648 issued as United States Patent No. 5,851,832 on December 22, 1998, with claims directed to central nervous system neural stem cell cultures and methods of proliferating them.

(3) USSN 08/486,307 issued as United States Patent No. 5,980,885 on November 9, 1999, with claims directed to growth factor-induced proliferation of neural stem cells *in vivo;*

(4) USSN 08/479,795 issued as U.S. Patent No. 6,071,889 on June 6, 2000, with claims directed to *in vivo* genetic modification of neural stem cells; and

(5) USSN 08/484,406 issued as U.S. Patent No. 6,294,346 on September 25, 2001, with claims directed to methods of screening biological agents.

A sixth related sister application, USSN 08/484,203, has been allowed -- the claims are directed to cDNA libraries prepared from neural stem cell cultures. All six of the above applications contain a specification identical to the above-identified application. All six have the same filing date as the above-identified application.

## ISSUES

Whether claims 26-27, 32-37 and 39-62 fail to meet the enablement requirement under 35 U.S.C. § 112, first paragraph.

## GROUPING OF CLAIMS

The claims stand or fall together.

## ARGUMENTS

Claims 26-27, 32-37, and 39-62, directed to methods of transplanting neural stem cell progeny, are pending in this application. There is a sole remaining rejection under 35 U.S.C. § 112, first paragraph, for lack of enablement. According to the Examiner, "[t]he claims are not enabled because the transplantation of multipotent neural stem cell progeny into a host has not been demonstrated to provide any therapeutic benefit to the host." Office Action, dated January 31, 2001, p. 3. The Examiner thus argues that the specification fails to teach "how to use" the claimed invention as required by 35 U.S.C. § 112, first paragraph. This rejection should be withdrawn on the basis of each and all of the arguments below. Applicants have submitted herewith the Declaration of Dr. Joseph Hammang (Hammang 2002 Decl. ¶ __).

First, the rejection is improperly made under § 112, first paragraph. Where, as here, the Examiner has questioned the therapeutic efficacy or benefit, the rejection is properly the subject of a § 101 utility rejection (with a concurrent § 112, first paragraph, rejection) on the basis that the claimed invention lacks a credible utility. See M.P.E.P. §§ 706.03(a)(1) and 2107 (and particularly the discussion of the relationship between § 101 utility rejections and § 112, first paragraph, rejections). Yet there is no § 101 rejection here -- to the contrary, the Examiner has acknowledged that the claimed methods meet the requirements of § 101 and have a credible utility.

Second, the "how to use" requirement of § 112, first paragraph, is satisfied if "the specification contains within it a connotation of how to use, and/or the art recognizes that

standard modes of administration are known and contemplated." M.P.E.P. § 2164.01(c). Applicants' specification meets this requirement (discussed in detail below).

Third, a rejection under § 112, first paragraph, is proper only if one reasonably skilled in the art could not make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *See United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). The voluminous art of record, and the declarations of Drs. Hammang, Baetge, Wahlberg and Uchida submitted July 30, 2001 (courtesy copies, without attachments, are provided as Exs. A-D), demonstrate that the ordinarily skilled artisan not only can but actually has routinely practiced the claimed methods and has, in fact, achieved a therapeutic benefit across a wide range of diseases and disorders.[1/] Further, the Examiner has ignored the teachings of the prior art, which indisputably teaches how to transplant neural cells and tissues (albeit not these neural stem cell cultures which applicants were first to invent). The "how to use" rejection cannot stand.

This Brief is organized as follows:

1. **The Rejection under § 112, First Paragraph Is Improper**
2. **The Specification Teaches One Skilled in the Art "How To Use" the Claimed Invention**
3. **One of Ordinary Skill in the Art Can and Has Used the Claimed Invention Without Undue Experimentation.**

## 1. The Rejection under § 112, First Paragraph Is Improper

The rejection under § 112, first paragraph, is based on the Examiner's assertion that transplantation according to the claimed methods does not provide a therapeutic benefit to the host. In short, the Examiner is questioning the efficacy of a claimed invention. This is not properly a "how to use" rejection -- it is a § 101 rejection. Under the case law and its interpretation in the M.P.E.P, a rejection that questions the efficacy of a claimed invention is properly analyzed as a utility rejection that must conform to the Utility Guidelines set forth in M.P.E.P. § 706.03(a)(1). Yet the Examiner has conceded that the claims have a credible utility and that the utility requirement has been met. M.P.E.P. § 706.03(a)(1) makes clear that if the

1/ Drs. Baetge and Hammang are named inventors and have intimate familiarity with the claimed methods; Drs. Wahlberg and Uchida have extensive experience in neural stem cell culture and neural stem cell transplantation and reflect the view of the ordinarily skilled artisan in that field.

Examiner determines that the claimed invention has a credible utility, the rejection may not be applied. *See* M.P.E.P. § 706.03(a)(1).

In considering what constitutes a "credible utility," the Guidelines provide that, to uphold a utility-based § 112, first paragraph, rejection, a case must represent one of those rare instances that meets the stringent criterion of being "totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555 (Fed. Cir. 1992), as discussed in the Legal Analysis accompanying the Utility Guidelines (M.P.E.P. § 2107). The only instances in which the Federal courts have found a lack of patentable utility were where, "based upon the factual record of the case, it was clear that the invention *could and did not work* as the inventor claimed it did." M.P.E.P. § 2107 (emphasis added). These rare cases have been ones in which the applicant either (a) failed to disclose any utility for the invention, or (b) asserted a utility that could be true only "if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." M.P.E.P. § 2107.01.

That is simply not the case here -- as is plain from the Hammang, Baetge, Uchida and Wahlberg Declarations submitted in July 2001, there are multiple scientific publications that confirm that transplantation of neural stem cell progeny according to the claimed methods can be routinely achieved. In addition, as is plain from the Declarations of record and the Hammang 2002 Declaration, such transplantation results in therapeutic benefit to the host. The Examiner has provided no evidence to the contrary.

In conformity with the Guidelines, Applicants asserted multiple utilities for neural stem cell cultures and specifically their utility in the transplantation methods claimed here. *See, e.g.*, Applicants' July 21, 1999, Response, p. 4, which discusses both the non-therapeutic uses as well as the therapeutic uses recited in the specification for the claimed methods. One of these utilities is in transplantation according to the claimed methods to provide a therapeutic benefit to the host -- and the Examiner has acknowledged this utility as credible.

The Utility Guidelines state that "data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process." M.P.E.P. §

2107.02(a).[2/] Applicants have provided voluminous evidence of record here establishing utility in a wide variety of animal neurotransplantation models (detailed below, in the Declarations of record, and in the Hammang 2002 Declaration).

The § 112 rejection was not properly made and should be withdrawn -- and the Examiner has conceded that Applicants have satisfied the requirements of § 101 with respect to the utility issue that the Examiner has raised by way of the improper § 112 rejection.

### 2. The Specification Teaches One Skilled in the Art "How To Use" the Claimed Invention

The Examiner alleges that the specification teaches that the only use for the claimed transplantation methods is to produce a therapeutic effect in the host. This is simply not true -- and the Examiner has ignored the teachings of the specification, specifically Examples 20 and 45, which clearly describe non-therapeutic transplantation according to the claimed methods. And, with no evidence to support the Examiner's position, the Examiner has flatly rejected all of Applicants' evidence demonstrating a therapeutic effect produce by the claimed methods.

The claims do ***not*** recite any requirement for providing a therapeutic benefit to a host. The claims recite a method of transplanting CNS neural stem cell cultures to a host, whether for non-therapeutic or therapeutic uses. The specification teaches ***both*** non-therapeutic ***and*** therapeutic uses for transplanting these neural stem cells (*see below*). Either use alone is sufficient to meet the enablement requirement. Both uses are met here.

***Non-Therapeutic Use***

The Examiner's determination that the claims are not enabled fails to follow the procedures set forth in the M.P.E.P.

M.P.E.P. § 2164.01(c) "How to Use the Claimed Invention" describes how a Patent Examiner must address issues of enablement:

> In contrast, when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation,

[2/] Consistent with this standard, in no case has a Federal court required an Applicant to support an asserted utility with data from human clinical trials. M.P.E.P. § 2107.02(d).

> sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention.

Here, the specification expressly teaches ***non-therapeutic*** transplantation for the non-therapeutic purpose of determining neural development events. See, e.g., Examples 20 and 45.[3/] The USPTO has acknowledged these enabled embodiments, stating that the specification "exemplifies the implantation of multipotent neural stem cell progeny into animal models." Office Action of January 21, 1999, Paper 29, pp. 3-4. The Examiner (at that time) also acknowledged that these CNS neural stem cells survive such transplantation. That Examiner further acknowledged that in this enabled embodiment, the transformed CNS neural stem cells transplanted into a host, in fact, produced β-galactosidase in the host. Since these embodiments are enabled, the M.P.E.P. directs that the claim is enabled. The rejection should be withdrawn on this basis alone.

***Therapeutic Use***

Notwithstanding that the claims do not require a therapeutic use, Applicants note that nonetheless, transplantation according to the claimed methods, in fact, produces a therapeutic benefit.

Therapeutic embodiments of the claimed transplantation methods are described throughout the specification. The specification contains detailed disclosure on how to transplant CNS neural stem cell cultures. See, *e.g.*, Specification, p. 36, line 10, to p. 42, line 13; p. 68, line 16, to p. 69, line 18; p. 78, line 17, to p. 71, line 6; and p. 96, line 12, to p. 97, line 28 for.

In addition, the specification also provides working examples of neural stem cell transplantation in various disease models, including, *e.g.*, myelin deficient disorders representative of neurodegenerative disorders such as Lou Gehrig's disease and Pelizaeus-Merzbacher disease, eye disorders such as human neuromyelitis optica, Huntington's disease, Parkinson's disease, cardiac arrest, stroke/ischaemia, epilepsy, Alzheimer's disease, and spinal cord injury and disease. *See, e.g.*, Specification, pp. 67-70, 96-101.

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3/ See, e.g., specification, pp. 72-74, EXAMPLE 20, and pp. 96-101, EXAMPLE 45 -- these two examples provide working examples of the transplantation of neural stem cells for the ***non-therapeutic*** use of determining neural developmental events.

Moreover, the specification also teaches and discloses the types of diseases to which the methods of the invention are directed. *See* Specification, p. 40, lines 9-18.

The specification also provides exemplary teaching of where to transplant the cells of the claimed invention. *See* Specification, p. 38, lines 17-30.

Further, the specification also teaches and discloses how to monitor the transplanted cells. *See* Specification, p. 39, lines 16-31.

In addition, each of the declarants of record has unequivocally stated that the ordinarily skilled artisan would know how to use the invention as claimed. See July 2001 Hammang Decl. ¶ 8; Wahlberg Decl. ¶ 8; Baetge Decl. ¶ 8; Uchida Decl. ¶ 8.

Applicants also note that skilled medical practitioners have routinely carried out cell and tissue neural transplantation as of the filing date of this application. Applicants refer the Board to Neural Grafting in the Mammalian CNS, Bjorklund and Stenevi, eds., (1985) Das, Ch. 3 pp. 23-30; Freed, Ch. 4, pp. 31-40; Stenevi et al., Ch. 5, pp. 41-50; Brundin et al., Ch. 6, pp. 51-60; David et al., Ch. 7, pp. 61-70; Seiger, Ch. 8, pp. 71-77 (1985). This reference (and numerous other references that cite to it), which was available at the earliest priority date of this application, provides detailed guidance relating to transplantation of cells into the central nervous system, *e.g.*, parenchymally, into the ventricular cavities or subdurally onto the surface of a host brain.

Indeed, such cell and tissue neurotransplantation protocols (well established at the priority date of this case) have become increasingly common. In short, methods of neural transplantation using cells or tissue can be and are administered in accordance with standard practices of medicine as of the filing date of this application. Dr. Wahlberg makes this plain in his declaration (submitted July 30, 2001):

> In addition, based on my personal experience, I believe that the ordinarily skilled artisan would know how to actually carry out the step of transplanting the neural stem cell cultures of this invention according to the claimed methods given that the art is replete with examples of transplantation of various other tissues or cells into various parts of the brain (witness, e.g., transplantation of porcine neural cells and fetal human cells). For this reason, in my view, it cannot be disputed that the ordinarily skilled artisan, with the specification in hand, would be able to transplant neural stem cell cultures into a host; that is, the ordinarily skilled artisan would know how to use the invention as claimed.

Wahlberg Decl. ¶ 8

Finally, Dr. Hammang's 2002 Declaration also notes that for years prior to Applicants' invention, neural cells and tissues have been transplanted using protocols well known at the 1991 filing date of this case. See, e.g., Hammang 2002 Decl., ¶ 14 and Exs. 6-8 attached thereto. Applicants' cells can be used in place of the prior art cells in the same transplantation protocols. No additional enablement is needed, and, as stated by the Federal Circuit in *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir. 1984): "A patent need not teach, and preferably omits, what is well known in the art."

Here the specification contains express disclosure of how to use the claimed invention.[4/] In addition, the specification and evidence of record clearly establishes that standard transplantation methodologies are known and contemplated, in accordance with M.P.E.P. § 2164.01(c).

For this reason too, Applicants have provided an enabling description of "how to use" the claimed invention. The rejection should be withdrawn.

### 3. One of Ordinary Skill in the Art Can and Has Used the Claimed Invention Without Undue Experimentation.

The Examiner has the burden to establish a reasonable basis to question the enablement for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); M.P.E.P § 2164.04. Under 35 U.S.C. § 112, first paragraph, lack of enablement is found only if one reasonably skilled in the art could not make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *See United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988); *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Even if the experimentation required is complex, it is not necessarily undue if

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4/ The Examiner apparently does not dispute that Applicants' specification adequately teaches how to carry out the first three steps of the claimed process, namely (1) obtaining a population of CNS stem cells, (2) culturing these stem cells and (3) inducing the proliferation of these stem cells. The only step of the claimed process left is the step of transplanting these stem cells into the patient/host. The methodology of how to perform this step is well know to the ordinarily skilled artisan. This is all that is required. The Examiner's enablement rejection is based on the Examiner's reading into this step a requirement for what appears to be a therapeutic benefit in humans since the Examiner has rejected all of Applicants' evidence of record in well-accepted animal models. This standard for enablement is not the law, and is flatly contradicted by M.P.E.P. § 2107.02(d).

artisans skilled in the relevant art typically engage in such experimentation. *See In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm. 1983).

The Examiner has not met this burden -- in fact, the Examiner has not produced any evidence at all. To the contrary, the only evidence of record here demonstrates that the claimed methods produce a therapeutic benefit. M.P.E.P. § 2104.01(a) requires that the Examiner consider this evidence, yet the Examiner has not done so.

Here, each of the declarants have stated that it is their view that the claimed methods are enabled and that the ordinarily skilled artisan would be able to routinely carry out the claimed transplant methods. See Hammang Decl. ¶ 4, 26; Wahlberg Decl. ¶ 4, 25; Baetge Decl. ¶ 4, 25; Uchida Decl. ¶ 4 (submitted July 30, 2001).

Applicants note that the specification provides an extraordinary amount of direction concerning how to practice the claimed invention (detailed above). And each of the declarants unequivocally concur that the specification provides ample guidance to the ordinarily skilled artisan -- see Hammang Decl. ¶ 8; Wahlberg Decl. ¶ 8; Baetge Decl. ¶ 8; Uchida Decl. ¶ 8 to carry out the claimed methods.

In addition to this direction concerning how to practice the invention, the inventors provided forty-five (45) *in vitro* and *in vivo* examples. Additionally, the specification teaches and discloses proliferation of the transplanted cells *in vivo*. See Specification, p. 52, line 14 – p. 47, line 26.

Finally, there is unrebutted evidence of record here demonstrating that the ordinarily skilled artisan would reasonably expect that the claimed transplantation methods would provide a therapeutic benefit because (1) the transplanted neural stem cell cultures secrete cellular products which are capable of providing a therapeutic benefit to the host, and (2) the neural stem cell cultures exhibit tissue-specific differentiation upon transplantation.

As each one of the Hammang, Baetge, Wahlberg and Uchida declarants have unequivocally stated, either of these facts would inescapably lead the ordinarily skilled artisan to conclude that transplantation of such neural stem cell cultures would have a reasonable expectation of success in providing a therapeutic benefit to the host. *See* Hammang Decl. ¶ 10; Wahlberg Decl. ¶ 10; Baetge Decl. ¶ 10; Uchida Decl. ¶ 10. The Examiner has provided no evidence to the contrary.

Specifically, transplantation according to the claimed methods produced a therapeutic benefit in numerous different well-accepted animal models, including evidence of record (in Hammang, Baetge, Uchida and Wahlberg July 2001 declaration) and also as reported in Dr. Hammang's 2002 Declaration. Outlined below is a summary of that evidence demonstrating that transplantation according to the claimed methods in fact provides a therapeutic benefit.

1. **delivery of a secreted cellular product to produce a therapeutic benefit of neuronal sprouting and sparing in a well accepted animal model of ischemia** (see Hammang Decl. ¶ 12; Wahlberg Decl. ¶ 12; Baetge Decl. ¶ 12; Uchida Decl. ¶ 12).

2. **delivery of a secreted cellular product to produce a therapeutic benefit of neuronal sprouting and sparing in a well accepted animal model of Huntington's disease** (see Hammang Decl. ¶ 14; Wahlberg Decl. ¶ 14; Baetge Decl. ¶ 14; Uchida Decl. ¶ 14).

3. **delivery of a secreted cellular product to produce a therapeutic benefit of neuronal sprouting and sparing in a well accepted animal model of Parkinson's disease** (see Hammang 2002 Decl. ¶ 8).

4. **transplantation to provide a therapeutic benefit of improved cognitive function in a well accepted animal model of age related cognitive deficit** (see Hammang Decl. ¶ 16; Wahlberg Decl. ¶ 16; Baetge Decl. ¶ 16; Uchida Decl. ¶ 16)

5. **transplantation to provide a therapeutic benefit of remyelination in a well accepted aminal model of a demyelinating disorder to provide near normal conduction velocities in the remyelinated axons** (see Hammang Decl. ¶ 17; Wahlberg Decl. ¶ 17; Baetge Decl. ¶ 17; Uchida Decl. ¶ 17). For additional discussion of other remyelination reports using the claimed methods and the therapeutic benefit conferred thereby, see Hammang Decl. ¶ 20-23; Wahlberg Decl. ¶ 20-22; Baetge Decl. ¶ 20-22.

6. **transplantation to provide a therapeutic benefit of neuronal repopulation in a well accepted animal model of retinal ischemia-reperfusion injury and mechanically injured adult retina** (see Hammang Decl. ¶ 18-19; Wahlberg Decl. ¶ 18-19; Baetge Decl. ¶ 18-19; Uchida Decl. ¶ 18-19)

7. **transplantation to provide a therapeutic benefit of replacing lost or deficient neural populations in a well accepted animal model** (see Hammang Decl. ¶ 24-26; Wahlberg Decl. ¶ 23-25; Baetge Decl. ¶ 23-25).

8. **transplantation to provide a therapeutic benefit of sparing neurons and host brain tissue from destruction due to ischaemia in a well accepted animal model** (see Hammang 2002 Decl. ¶ 10).

9. **transplantation to provide a therapeutic benefit of improved spatial recognition in a well accepted animal model of ischaemia** (see Hammang 2002 Decl. ¶ 11).

10. **transplantation to provide therapeutic benefit of neuronal replacement and continued nNOS production in a well accepted animal model of disorders of the enteric nervous system** (see Hammang 2002 Decl. ¶ 12).

11. **transplantation to provide a therapeutic benefit of amelioration of the extent of radiation-induced myelopathy in spinal cord in a well accepted animal model** (see Hammang 2002 Decl. ¶ 13).

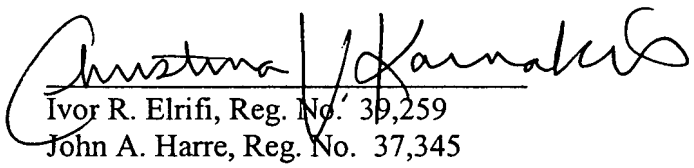
In addition, the declarants have referred to additional publications that in their view reflect the view of the art that the claimed methods would provide a therapeutic benefit to the host. *See* Hammang Decl. ¶ 27; Wahlberg Decl. ¶ 26; Baetge Decl. ¶ 26; Uchida Decl. ¶ 20. In sum, there is voluminous evidence that the claimed methods do, in fact, produce a therapeutic benefit. This evidence is unrefuted -- indeed the Examiner has not produced any evidence whatsoever to support the enablement rejection.

For all the foregoing reasons, the rejection should be withdrawn because the pending claims are enabled.

## CONCLUSION

For all and each of the foregoing reasons, this appeal should be allowed and the Examiner's rejection under 35 U.S.C. § 112, first paragraph, should be reversed.

Respectfully submitted,



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## APPENDIX 1: CLAIMS ON APPEAL

26. A method of transplanting neural stem cell progeny to a host comprising:

(a) obtaining a population of cells derived from mammalian neural tissue containing at least one multipotent CNS neural stem cell, said neural stem cell under suitable culture conditions producing progeny that differentiate into neurons that express neuron specific enolase or neurofilament and glia that express glial fibrillary acidic protein or express galactocerebroside;

(b) culturing the neural stem cell in (a) in a culture medium containing one or more growth factors which under suitable culture conditions induces multipotent neural stem cell proliferation;

(c) inducing proliferation of said multipotent neural stem cell to produce neural stem cell progeny which includes multipotent neural stem cell progeny cells; and

(d) transplanting said multipotent neural stem cell progeny to said host.

27. The method of claim 26 wherein prior to step (d), said neural stem cell progeny are genetically modified to express a biological agent selected from the group consisting of growth factors, growth factor receptors, neurotransmitters, neurotransmitter synthesizing genes, neuropeptides, and chromaffin granule amine transporter.

32. The method of claim 26 wherein said CNS neural stem cells are maintained in a culture medium containing one or more growth factors selected from the group consisting of epidermal growth factor, amphiregulin, acidic fibroblast growth factor, basic fibroblast growth factor, transforming growth factor alpha, and combinations thereof.

33. The method of claim 32 wherein said one or more growth factors in the culture medium in (b) is epidermal growth factor.

34. The method of claim 32, wherein said one or more growth factors in the culture medium in (b) is selected from the group consisting of acidic fibroblast growth factor, basic fibroblast growth factor, and combinations thereof.

35. The method of claim 34 wherein said culture medium additionally contains epidermal growth factor.

36. The method of claim 26 wherein the cells obtained in (a) are not treated with serum *in vitro*.

37. The method of claim 26 wherein prior to (d), at least one subsequent cell culture is prepared by combining said neural stem cell progeny with fresh culture medium containing one or more growth factors capable of inducing multipotent CNS neural stem cell proliferation to proliferate said multipotent CNS neural stem progeny cells to produce more multipotent CNS neural stem progeny cells.

39. The method of claim 26 wherein prior to (d), said multipotent CNS neural stem cell progeny are induced to differentiate into differentiated neural cells.

40. The method of claim 39 wherein said differentiated neural cells are selected from the group consisting of neurons that express neuron specific enolase or neurofilament and glia that express glial fibrillary acidic protein or express galactocerebroside.

41. The method of claim 26 wherein said neural stem cell progeny are transplanted to said host's central nervous system.

42. The method of claim 41 wherein said neural stem cell progeny are transplanted to said host's spinal cord.

43. The method of claim 41 wherein said neural stem cell progeny are transplanted to said host's striatum.

44. The method of claim 41 wherein said neural stem cell progeny are transplanted to said host's hippocampus.

45. The method of claim 41 wherein said neural stem cell progeny are transplanted into said host's frontal cortex.

46. The method of claim 41 wherein said neural stem cell progeny are transplanted into said host's parietal cortex.

47. The method of claim 41 wherein said neural stem cell progeny are transplanted to a lesioned region of said host's central nervous system.

48. The method of claim 26 wherein said cells obtained in (a) are obtained from said host's neural tissue.

49. The method of claim 26 wherein said cells obtained in (a) are derived from juvenile or adult mammalian neural tissue.

50. The method of claim 26 wherein said cells obtained in (a) are derived from human neural tissue.

51. The method of claim 26 wherein said mammalian neural tissue in (a) is selected from the group consisting of cerebral cortex tissue, cerebellum tissue, midbrain tissue, brainstem tissue, spinal cord tissue, ventricular tissue, frontal lobe tissue, conus medullaris tissue, hypothalamus tissue, and combinations thereof.

52. A method of transplanting neural stem cell progeny to a host comprising:

a) obtaining an *in vitro* cell culture comprising mammalian CNS neural stem cells, wherein one or more cells in the culture (i) proliferates in a culture medium supplemented with one or more mitogens, (ii) retains the capacity for renewed proliferation, and (iii) maintains the multipotential capacity, under suitable culture conditions, to differentiate into neurons, astrocytes, and oligodendrocytes;

b) transplanting said one or more cells to said host.

53. The method of claim 52 wherein the mammalian CNS neural stem cells are derived from adult mammalian CNS.

54. The method of claim 53 wherein the mammalian CNS neural stem cells are derived from human mammalian CNS.

55. The method of claim 52, wherein the mitogen is a growth factor selected from the group consisting of epidermal growth factor, amphiregulin, acidic fibroblast growth factor, basic fibroblast growth factor, transforming growth factor alpha, and combinations thereof.

56. The method of claim 52, wherein the mitogen is a growth factor selected from the group consisting of epidermal growth factor, basic fibroblast growth factor, and combinations thereof.

57. The method of claim 52, wherein the mitogen is epidermal growth factor.

58. The method of claim 52, wherein the mitogen is basic fibroblast growth factor.

59. The method of claim 52, wherein the cells form a suspension culture.

60. The method of claim 59, wherein the CNS neural stem cells, in the presence of differentiation-inducing conditions or an appropriate tissue environment, produce progeny cells that differentiate into neurons, astrocytes, and oligodendrocytes.

61. The method of claim 60, wherein said differentiation-inducing conditions are *in vitro*.

62. The method of claim 60, wherein said differentiation-inducing conditions are *in vivo*.

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